

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference 97 799 a/ubr	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/EP 03/03060	International filing date (day/month/year) 24.03.2003	Priority date (day/month/year) 27.03.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/44		
Applicant FUJISAWA DEUTSCHLAND GMBH et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 22.10.2003	Date of completion of this report 19.03.2004
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Bonzano, C Telephone No. +31 70 340-2202 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP 03/03060

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-35 as originally filed

Claims, Numbers

1-14 as originally filed

Drawings, Sheets

1/3-3/3 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
4. The amendments have resulted in the cancellation of:
- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP 03/03060

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-9,11,12,14

because:

☒ the said international application, or the said claims Nos. 14, with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-9,11,12 partially

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	-
	No: Claims	1-14
Inventive step (IS)	Yes: Claims	-
	No: Claims	1-14
Industrial applicability (IA)	Yes: Claims	see separate sheet
	No: Claims	

2. Citations and explanations

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/03060**

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. No International Preliminary Examination Report will be given in respect of subject-matter which is not covered by the search report (Rule 66(1)(e) PCT).
2. The subject matter of claim 14 concerns a method of treatment of the human/animal body which is considered by this Authority to be covered by the provisions of Rule 67.1 (IV) PCT. Consequently, no International Preliminary Examination Report will be formulated with respect to the industrial applicability of the subject matter of these claims (Article 34(4) (a)(I)PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3. The applicant's attention is drawn to the fact that the present International Preliminary Examination Report expressed as to the novelty, inventive step and industrial applicability refers only to the matter for which an International Search Report has been drawn up (i.e. cancer, psoriasis, arthritis, inflammation).
4. Claims 1-9, 11, 12 relate to the treatment of diseases and to diagnostic applications which are actually not well defined. The use of the definitions "inhibition or reduction of angiogenesis, disease responding to inhibition or reduction of angiogenesis, disease responding to inhibition or reduction of VEGF production; in vitro diagnostic method" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT.
Although the influence of a compound on the angiogenesis is indisputably a pharmacological effect, it cannot in itself be considered a therapeutic application. There are an undefined number of diseases which might be related to this pharmacological effect. In other terms, it still needs to find a practical application in the form of a defined treatment of a specified pathological condition, this being an essential technical feature, in order to render the claims clear.
Moreover, the claims cover all diseases responding to inhibition or reduction of angiogenesis and all in vitro diagnostic methods, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such diseases and diagnostic methods. In the

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP03/03060

present case, the claims lack support, and the application lacks disclosure.

5. Reference is made to the following documents:

- D1: DE 196 24 659 A (KLINGE CO CHEM PHARM FAB) 8 January 1998 (1998-01-08)
- D2: DE 197 56 235 A (KLINGE CO CHEM PHARM FAB) 1 July 1999 (1999-07-01)
- D3: DE 196 24 704 A (KLINGE CO CHEM PHARM FAB) 8 January 1998 (1998-01-08)
- D4: DE 197 56 212 A (KLINGE CO CHEM PHARM FAB) 1 July 1999 (1999-07-01)
- D5: DE 197 56 236 A (KLINGE CO CHEM PHARM FAB) 1 July 1999 (1999-07-01)
- D6: US-A-4 778 796 (UNO HITOSHI ET AL) 18 October 1988 (1988-10-18)
- D7: DE 197 56 261 A (KLINGE CO CHEM PHARM FAB) 1 July 1999 (1999-07-01)
- D8: NIE DAOTAI ET AL: 'Eicosanoid regulation of angiogenesis: Role of endothelial arachidonate 12-lipoxygenase.' BLOOD, vol. 95, no. 7, 1 April 2000 (2000-04-01), pages 2304-2311, XP002208812 ISSN: 0006-4971
- D9: COLAVITTI RENATA ET AL: 'Reactive oxygen species as downstream mediators of angiogenic signaling by vascular endothelial growth factor receptor-2/KDR.' JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 277, no. 5, February 2002 (2002-02), pages 3101-3108, XP001074657 February, 2002 ISSN: 0021-9258
- D10: NISHIKAWA ET AL: 'Acrylamide derivatives as antiallergic agents. 2. Synthesis and structure activity relationships of N-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-(3-pyridyl)acrylamide s' JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 32, no. 3, 1989, pages 583-593, XP002101517 ISSN: 0022-2623

Unless otherwise specified, reference is made to the passages cited in the search report.

6. For the assessment of the present claims 1-14 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO,

for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Novelty

7. The documents D1-D4 disclose the use of the compounds corresponding to formula I, in particular mentioned in claim 7 (D1-D3), for treating psoriasis, tumours, lymphoms. They are also defined as being cytostatics and cancerostatics (see D1: page 77, lines 20-48; page 64, examples 150,153,158,159,162; page 2, lines 1-26; page 77, line 51-page 78, line 32; D2: page 33, examples 82,120; page 74, line 40-page 75, line 41; D3: page 78, line 1 - page 79, line 7). Document D6 relates to compounds as claimed in claim 1, similar to the compounds of claim 8 for treating arthritis and inflammation (see D6: page 2, line 21-50; page 38).

Document D5 discloses compounds of formula I, having a structure similar to the compounds claimed in claim 8, for treating psoriasis, autoimmune diseases and tumors.

The mere explanation of an effect obtained when using a compound in a known process, even if the explanation relates to a pharmaceutical effect which was not known for that compound, cannot confer novelty to said process. In the present case, the newly discovered technical effect of reducing angiogenesis does not confer novelty on the claims directed to the use of a known compound corresponding to formula I for a known purpose (treatment of cancer, psoriasis, arthritis, inflammation). No novelty exists, if the claim is directed to the use of a known compound for a known purpose, even if a newly discovered technical effect (the reduction of angiogenesis) underlying said known use is indicated in that claim. The subject-matter of claims 1-14 is therefore not new and does not satisfy the criterion set forth in Article 33(2) PCT.

Inventive step

8.1 The present claimed subject matter, as far as novel, appears to be obvious over the above mentioned documents.

8.2 Document D8, which is considered to represent the most relevant state of the art, reports that angiogenesis is mediated by the activity of lipoxxygenase: it suggests

the role of lipoxygenase inhibitors for treating angiogenesis mediated diseases. Moreover it is pointed out that a lipoxygenase inhibitor can counteract the effects of VEGF (see D8: page 2310, column 2, paragraph 4; column 1, paragraph 1).

The present application differs in that the lipoxygenase inhibitors used with the specific purpose of inhibiting angiogenesis are the compounds of formula I.

The problem to be solved with respect to D8 is therefore to find an alternative lipoxygenase inhibitor for treating angiogenesis mediated diseases.

Documents D7 and D10 describe the activity of the claimed compounds as lipoxygenase inhibitors. In particular D10 discloses the compounds mentioned in claim 8. (see D7: column 24, example 85, 91; column 1, lines 7-37; D10: page 588, compounds 1a,21; page 583, column 1).

It is common knowledge for the man skilled in the art that VEGF is the major angiogenic factor produced by tumor cells (see D9: page 3101, column: 2, paragraph 3).

Therefore, being aware that lipoxygenase inhibitors are useful for inhibiting angiogenesis and for reducing the effects of VEGF, and knowing that the compounds of formula 1 are lipoxygenase inhibitors, the person skilled in the art would have been inevitably led to use the pyridine derivatives of formula 1, and in particular of claim 8 of the present invention for reducing angiogenesis. Due to their well known lipoxygenase inhibitor activity, the skilled person would have expected for the compounds of formula 1 the same effect on angiogenesis as the lipoxygenase inhibitors described in D8.

Moreover, document D8 discloses that inflammation, tumor, retinopathy are pathologic conditions related to angiogenesis; and D9 points out the relation between angiogenesis and the production of VEGF.

This teaching would strengthen the motivation of the person skilled in the art, to use the same compounds, counteracting the effects of VEGF and known for treating inflammations and tumors, also for reducing angiogenesis.

3.3 Thus, the subject-matter of claims 1-14 does not involve an inventive step and does not satisfy the criterion set forth in Articles 33(3) PCT. Moreover, only examples concerning the treatment of cancer are given.